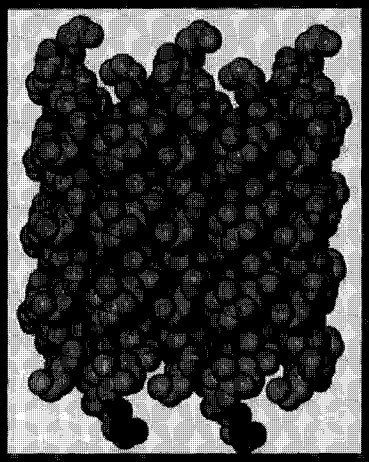
EXHIBIT Z

SOLID-STATE CHEMISTRY OF DRUGS



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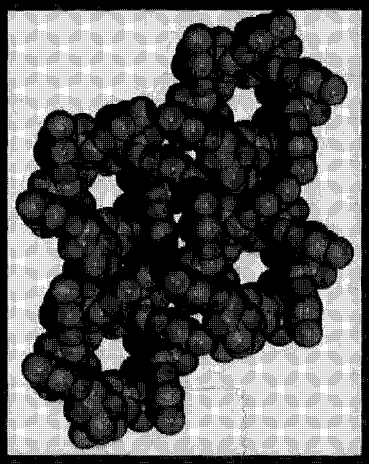

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SSCI, Inc., 3065 Kent Avenue, West Lafayette, Indiana 47906-1076
www.ssci-inc.com

Printed in the United States of America
Printing History: 03 02 01 00 99 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data

Byrn, Stephen R.
Solid-State Chemistry of Drugs / Stephen R. Byrn, Ralph R. Pfeiffer, Joseph G. Stowell—2nd ed.
xvii, 576 p. :ill.; 24 cm.
Includes bibliographical references and index.
ISBN 0-967-06710-3
ISBN 0-967-06711-1 (paperback student edition only)
1. Pharmaceutical Chemistry. 2. Solid state chemistry. 3. Chemistry, Pharmaceutical. I. Title.
QV744.B995s 1999
615'.19

The publisher offers a discount paperback edition of this book to registered students only. Quantity discounts on the hardover edition are also vailable.

Printed on acid-free paper.

Cover illustration: The figures are space-filling representations of prednisolone 21-*tert*-butylacetate crystal packing diagrams. On the top is Form IV illustrating the densely packed crystal lattice. On the bottom is Form V showing the oxygen-accessible tunnels produced by desolvation.

1

Drugs as Molecular Solids

This chapter provides a general overview of solid-state chemistry of drugs. Specifically, it treats the impact on pharmaceuticals of solid-state chemistry, the crystalline state, amorphous solids, moisture uptake, patents, and physical as well as chemical transformations. In many cases, a subject is introduced in this chapter and addressed in depth in a later chapter. It is hoped that the reader will gain an appreciation of what this discipline encompasses by reading this chapter.

1.1 ROLE OF SOLID-STATE TECHNOLOGY IN THE PHARMACEUTICAL INDUSTRY

Figure 1.1 depicts the central role that solid-state research plays in the pharmaceutical industry. Reflection on the part of anyone even slightly familiar with the industry will confirm many of the connections shown in Figure 1.1, but some specific examples will further point out how important these connections can be in given cases.

Solid pharmaceuticals exist as **polymorphs**, **solvates**, or in **amorphous** forms, collectively described as **solid forms**. Figure 1.2 shows the solubility behavior of two polymorphs with time. It is clear that the solubility of each of the solid forms is decreasing because of the crystallization of a more stable crystal form (Carless *et al.*, 1968). Thus, this figure illustrates the effect of polymorphic change on **suspension** stability. Obviously these changes reflect on the stability of the product as well as

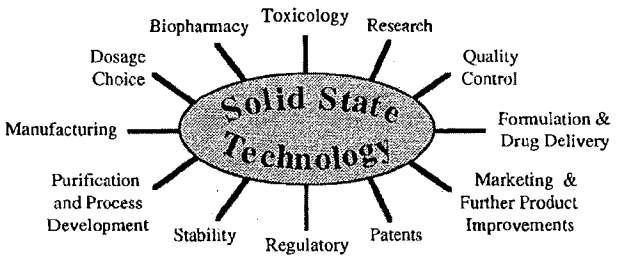


Figure 1.1 A diagram of the role of solid-state studies in the pharmaceutical industry.

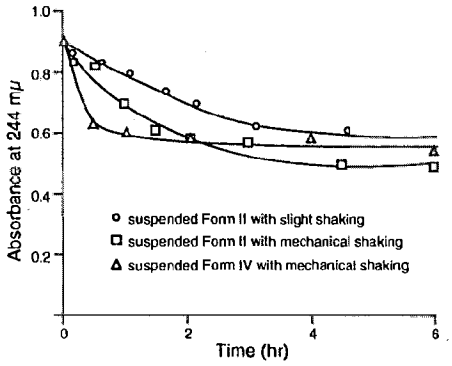


Figure 1.2 Decrease in absorbance of a cortisone acetate Form II solution in the presence of suspended Form II or Form IV as a function of time (Carless *et al.*, 1968).

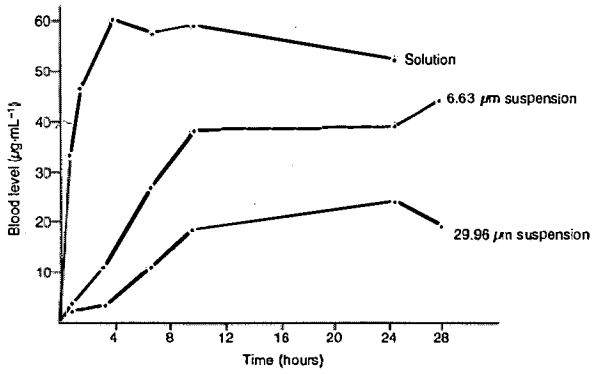
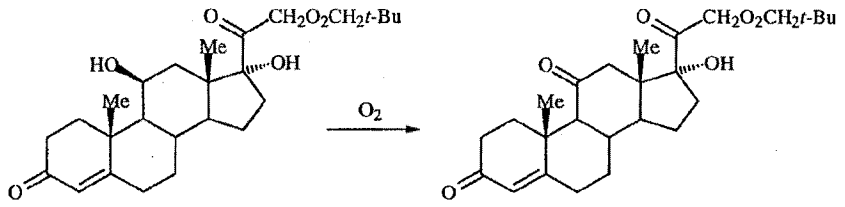


Figure 1.3 Blood levels of phenobarbitone versus time after intramuscular injection of two preparations with different particle sizes (redrawn from Miller and Fincher 1971).

regulatory issues, quality control, **formulation**, and drug bioavailability. Figure 1.3 depicts the effect of particle size on the **dissolution rate** of phenobarbitone and illustrates the role of solid-state technology in the formulation and **drug delivery**, quality control, and regulatory areas.

Studies of hydrocortisone *tert*-butylacetate and prednisolone *tert*-butylacetate (Byrn *et al.*, 1988; Lin *et al.*, 1982) and dihydrophenylalanine (Ressler, 1972) show that different crystal forms of these substances have different chemical reactivity. For example, the hexagonal crystal form of both hydrocortisone *tert*-butylacetate and prednisolone *tert*-butylacetate oxidizes in the solid state whereas the other crystal forms of these two pharmaceuticals are chemically stable.

The shape and particle size of the solid drug substance can have an important effect on the **flowability**, **syringeability**, **filterability**, **tableting behavior**, and **bulk density** of the drug. For example a suspension of plate-shaped crystals may be in-



hydrocortisone 21-*tert*-butylacetate **cortisone 21-*tert*-butylacetate**

jected through a small needle with greater ease than one of needle-shaped crystals. Similarly, the tableting behavior of plate-shaped crystals would differ from that of needle-shaped crystals. Furthermore, the shape and size of the particles is generally related to the internal crystal structure of the solid. Thus, the internal structure of the solid material can dramatically influence the bulk properties of the drug. These properties in turn relate to formulation, manufacturing, patents, quality control, regulatory, and possibly other areas indicated in Figure 1.1.

1.2 THE CRYSTALLINE STATE: BASIC CONCEPTS

An understanding of the solid-state chemistry of drugs begins with a statement of several general points:

- most drugs are used in a crystalline form
- crystals are held together by molecular forces
- the arrangement of molecules in a crystal determine its physical properties
- the physical properties of a drug can affect its performance

We can then proceed to learn how an understanding of the crystalline state leads to understanding of drug properties. (A treatment of non-crystalline, or amorphous, solids is given in Chapter 12.)

To accommodate the general reader in following this discussion of the crystalline state, brief definitions of some terms are listed in a glossary at the end of the book. Many of the terms may require further explanations which will be given when appropriate.

A. PACKING AND SYMMETRY

One definition of a crystal is that of a solid in which the component molecules are arranged, or "packed," in a highly ordered fashion. When the specific local order, defined by the **unit cell**, is rigorously preserved without interruption throughout the boundaries of a given particle, that particle is called a **single crystal**. This ordered packing leads to a structure with very little **void space**, which explains why most substances are more dense in their solid state than in their liquid state. By way of illustration, Figure 1.4 shows a projection of a unit cell and also shows how tightly the molecules are packed in a typical crystalline substance such as glycine.

Looking at this example and contemplating the enormous number of crystalline compounds known to modern science, not to mention those to be discovered, it be-

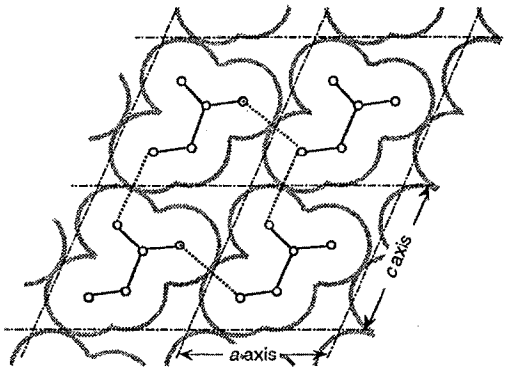


Figure 1.4 A close packed layer of glycine molecules in a crystal projected on the *ac* plane. The heavy gray lines show the van der Waals radii of the atoms (the hydrogens have been omitted for clarity).

comes obvious there must be a remarkable variety of structures found in different crystals. What factors, then, determine the crystal structure of a given compound?

When the question "In how many different ways can varied-shaped molecules be packed?" is put on a mathematical basis, it has been shown that certain **symmetry elements** (or, **symmetry operations**) are involved and that all possible combinations of these can be summarized in exactly 230 ways, called **space groups**. The symmetry operations are listed in Table 1.1. Formal representations of the 230 space groups, which encompass all seven **crystal systems** and all possible combinations of symmetry operations, are found in the *International Tables for Crystallography* (1987).

To understand how the packing of a crystal structure is described by the symmetry operations of the space group it may be helpful to regard the following example (see Figure 1.5). Figure 1.5 shows a diagram of the symmetry elements in space group *Pmm*2. The *P* means that the space group is **primitive** rather than **body-centered** or **face-centered**. The *mm*2 means that the cell contains **mirror planes** (*m*) perpen-

Table 1.1 The Symmetry Elements of Crystal Packing[a]

Symmetry Element	Description
rotation axis	When a rotation of 360°/*n* results in the same structure, then the crystal contains an *n*-fold rotation axis. For crystals, *n* is restricted to 1, 2, 3, 4, and 6.
screw axis	An *n*-fold screw axis exists when a rotation of 360°/*n* followed by a translation parallel to the axis of rotation brings the structure into coincidence.
rotatory-inversion axis	An *n*-fold rotatory-inversion axis exists when a rotation of 360°/*n* followed by inversion results in the same structure.
mirror plane	A mirror plane exists when a reflection through that plane results in the same structure.
glide plane	A glide plane exists when reflection through a mirror plane followed by translation brings the structure into coincidence.

a Note that a crystal containing only one enantiomer of a chiral compound cannot fall into a space group containing any one of the last three symmetry elements in Table 1.1.

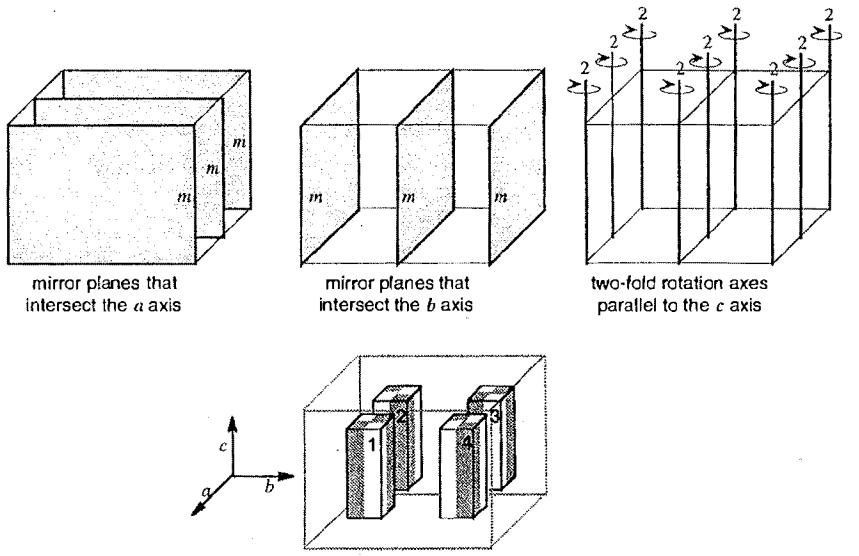


Figure 1.5 Symmetry elements for space group *Pmm*2.

dicular to both the *a* and *b* axes and a **two-fold rotation axis** along the *c* axis.

Taking block 1 at position (x,y,z) and reflecting it across the mirror that intersects the *a* axis at ½*a*, block 2 is obtained. Reflecting block 2 across the mirror that intersects the *b* axis at ½*b* generates block 3, and block 4 results from block 3 being reflected across the mirror at ½*a*. [In actual cases, of course, these blocks are molecules, but the operations are the same and thus the *x*, *y*, *z* coordinates of each atom in molecule 1 are translated to the corresponding $(1-x,y,z)$ in the first step, to $(1-x,1-y,z)$ in the next step, and $(x,1-y,z)$ in the last step.] Note that this combination of mirror planes necessarily creates the two-fold rotation axes parallel to the *c* axis. These steps, in any order, are continued into the neighboring unit cells. In this exercise we are, in a sense, mimicking actual crystal growth.

B: Forces Responsible for Crystal Packing

At this point, it is appropriate to consider the forces responsible for holding crystals together. **Ionic crystals** are held together by **ionic bonds** while **organic crystals** are held together largely by **non-covalent interactions**. These non-covalent interactions are either hydrogen-bonding or **non-covalent attractive forces**. Both hydrogen-bonding and non-covalent attractive interactions result in the formation of a regular arrangement of molecules in the crystal. **Non-covalent attractive interactions**, which are sometimes called **non-bonded interactions**, depend on the dipole moments, polarizability, and electronic distribution of the molecules. Hydrogen bonding, of course, requires donor and acceptor functional groups. Another important factor is the symmetry of the molecules. Kitaigorodskii (1961) provided a review of the forces holding crystals together in his classic book *Organic Chemical Crystallography*. The two-

volume *Structure Correlations* (Bürgi and Dunitz, 1994) describes in detail the modern view of crystal packing.

The symmetry (or lack of symmetry) of a molecule determines how it is packed in the crystal and, in some cases, determines the overall symmetry of the crystal. Molecules with symmetries that allow them to fit together in a close-packed arrangement generally form better crystals and crystallize more easily than irregular molecules. This factor is not always evident from molecular models.

Several researchers have described crystal packing forces in specific classes of compounds. Reutzel and Etter (1992) evaluated the conformational, hydrogen-bonding, and crystal-packing forces of acyclic imides. Crystal-packing forces in biphenyl fragments were evaluated by Brock and Minton (1989); Gavezzotti and Desiraju (1988) have analyzed packing energies and packing parameters for fused-ring aromatic hydrocarbons.

Kitaigorodskii (1961) has advanced the **close-packing theory** to explain the forces holding crystals together. He suggested that the basic factor that affects free energy is the packing density which affects ΔH, enthalpy. The denser or more closely packed crystal has the smaller free energy. This means that the heat of sublimation (and, to a first approximation, melting point) increases as the packing density increases and, that in a series of polymorphs, the densest polymorph is the most stable. This is the molecular basis of the **density rule** which states that if one modification of a molecular crystal has a lower density than the other, it may be assumed to be less stable at absolute zero (Burger and Ramberger, 1979a). However, it is important to note that there are exceptions to this rule. Some exceptions probably arise because strong hydrogen bonds can negate less dense packing (*e.g.*, ice) thereby causing the less dense polymorph to be more thermodynamically more stable (Burger and Ramberger, 1979a–b). Brock *et al.*(1991) studied the validity of **Wallach's rule**, which states that the racemic crystals of a pair of enantiomers are denser and thus more stable than crystals of the individual enantiomers, and showed that, for the 65 chiral/racemic pairs investigated, the racemic crystals are only ~1% more dense than the corresponding chiral crystals (yet the racemates are less dense for many individual pairs).

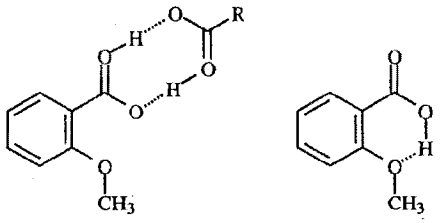
Kitaigorodskii (1961) also pointed out the importance of symmetry which affects ΔS, entropy. The free energy of a crystal undoubtedly increases as the number of crystallographically **independent molecules** in the crystal increases. Thus high symmetry, which reduces the number of independent molecules in a crystal, *increases* the free energy of the crystal and conflicts with the *reduction* in free energy gained from close packing. The magnitude of these opposing effects varies from structure to structure.

C. Hydrogen Bonding

Of the various forces that hold organic molecules in the solid, hydrogen bonding is perhaps the most important. Etter (1990) has reviewed the extent and types of hydrogen bonding that can exist in solids and pointed out that polar organic molecules in solution tend to form hydrogen-bonded aggregates. These aggregates are precursors to the crystals which form when the solution is supersaturated. This concept helps to explain the many different hydrogen-bonding motifs seen in different solids.

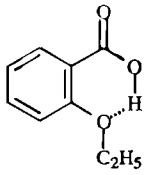
Several different types of carboxylic acids have been studied. For example, in *o*-alkoxybenzoic acids, the presence of dimers or the formation of intramolecular hydrogen bonds depends on the state of the sample. In *o*-anisic acid, dimers are observed in

the solid state while intramolecular hydrogen bonds are observed in dilute solution. However, in *o*-ethoxybenzoic acid, only intramolecular hydrogen bonds are observed in both the solid state and in solution (Etter, 1990).



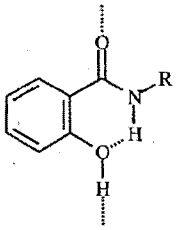
***o*-methoxybenzoic acid**
in the solid state

in solution

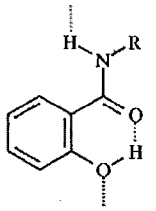


***o*-ethoxybenzoic acid**
in solution and in the solid state

Etter *et al.* (1988) also studied the hydrogen bonding in salicylamide derivatives and pointed out that two types of hydrogen bonding patterns are possible in these compounds. One pattern involves an intramolecular —N—H···OH— hydrogen bond and an intermolecular —O—H···O=C hydrogen bond while the other pattern involves an intermolecular —N—H···OH— hydrogen bond and an intramolecular —O—H···O=C hydrogen bond.



Intra: NH···OH
Inter: C=O···HO



Intra: C=O···HO
Inter: NH···OH

Etter and co-workers (1990a) defined a system which uses a graph set to classify and symbolically represent the different types of hydrogen bonds that can be formed. A short representation of the different graph sets is shown in Figure 1.6. A graph set motif designator (C for intermolecular chains or **catemers**, R for intermolecular rings, D for discrete or other finite sets, and S for intramolecular hydrogen bonds) is assigned by identifying the size or degree of the hydrogen-bond pattern G, the number of acceptors a, the number of donors d, and the total number of atoms n in that pattern. This designation takes the form: $G_d^a(n)$.

Etter (1990b) also developed rules governing hydrogen bonding in solid organic compounds. Hydrogen-bond donors and acceptors in solids are classified either as "reliable" or "occasional" donors and acceptors and are listed in Table 1.2. Using these classifications, three rules were devised:

1. All reliable proton donors and acceptors are used in hydrogen bonding.
2. Six-membered ring *intra*molecular hydrogen bonds form in preference to *inter*molecular hydrogen bonds.

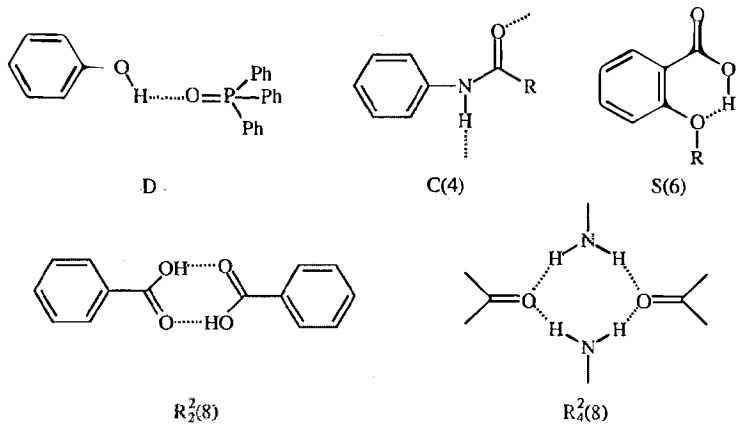


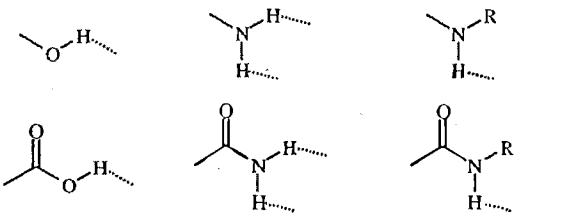
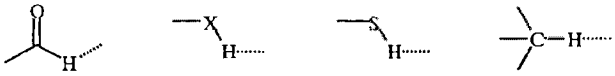
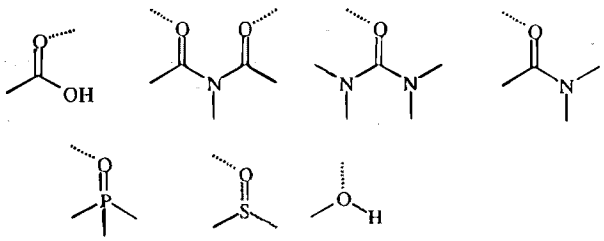
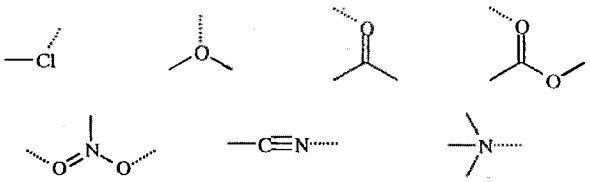
Figure 1.6 Etter graph sets describing different hydrogen bond motifs where D designates a discrete or other finite set, C a chain or catemer, S an intramolecular ring, and R designates an intermolecular ring. The number of hydrogen-bond acceptors in rings is superscripted, the number of hydrogen-bond donors is subscripted, and the total number of atoms in the hydrogen-bond pattern is in parentheses (Etter, 1990; Bernstein *et al.*, 1995).

3. The best proton donors and acceptors remaining after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds.

These rules apply quite well to hydrogen bonding of small molecules. However, in some larger molecules (*e.g.*, erythromycins), factors dictated by the geometry of the molecule as well as the large number of donors and acceptors present may make it impossible to satisfy all these rules.

It has been demonstrated that the systematic study of **cocrystals** (crystals which contain an ordered arrangement of two different neutral molecules that are not solvent molecules) can lead to insight concerning the factors influencing hydrogen bonding in crystals (Etter and Baures, 1988; Etter *et al.*, 1990a–b, Etter and Adsmond, 1990; Etter and Reutzel, 1991). An important aspect of this research into hydrogen bonding is the realization that cocrystals can form and crystallize from certain solutions that contain more than one molecular species. (Cocrystals are often formed between hydrogen-bond donor molecules and hydrogen-bond acceptor molecules) The geometry and nature of hydrogen bonding in cocrystals can be described using the above rules. Among the cocrystals studied by Etter's group were cocrystals involving ureas with ketones, carboxylic acids with 2-aminopyridine (see Figure 1.7), as well as adenine or cytosine with many acidic organic compounds including carboxylic and *N*-acyl-amino acids. The urea cocrystals are especially interesting because so many can be studied. Other cocrystal systems investigated by Etter's group include:

Table 1.2 Reliable and Occasional Hydrogen Bond Donors and Acceptors

Type	Functional Group Involved
Reliable Donor	
Occasional Donor	
Reliable Acceptors	
Occasional Acceptors	

Etter, 1990; Bernstein *et al.*, 1995

pyrimidines, pyridines ..... carboxylic acids
pyridine-*N*-oxides ..... acids, alcohols, amines
triphenylphosphine oxides ..... acids, amides, alcohols, ureas, sulfonamides, amines, water
carboxylic acids ..... other carboxylic acids, amides
m-dinitrophenylureas ..... acids, ethers, phosphine oxides, sulfoxides, nitroanilines
imides ..... other imides, amides

The formation of cocrystals may also be important in explaining certain drug-excipient interactions.

Panunto *et al.* (1987) have reviewed hydrogen bond formation in crystalline nitroanilines. They showed that hydrogen bonding occurred between the amino group and the nitro group even though the nitro group is only an occasional acceptor. In general, they found that the donor hydrogen from the amino group is placed equidistant

between the acceptor oxygens of the nitro group. The geometry of this interaction appears to be controlled by the lone pair directionality of the nitro groups.

This elegant work by Etter on graph set definitions and qualitative hydrogen-bonding rules can greatly assist the understanding of the interaction of molecules in the solid state and presumably also in solution. Further discussion of hydrogen bonding in salts is included in Chapter 5.

1.3 A Given Substance can Crystallize in Different Ways

Apart from exhibiting differences in size, crystals of a substance from different sources can vary greatly in their shape. Typical particles in different samples may resemble, for example, needles, rods, plates, prisms, etc. Such differences in shape are collectively referred to as differences in **morphology**. This term merely acknowledges the fact of different shapes: it does not distinguish among the many possible reasons for the different shapes.

Naturally, when different compounds are involved, different crystal shapes would be expected as a matter of course. When batches of the *same substance* display crystals with different morphology, however, further work is needed to determine whether the different shapes are indicative of polymorphs, solvates or just **habits**. Because these distinctions can have a profound impact on drug performance, their careful definition is very important to our discourse. At this time, only brief definitions are presented, but an exhaustive treatment of each will be given later.

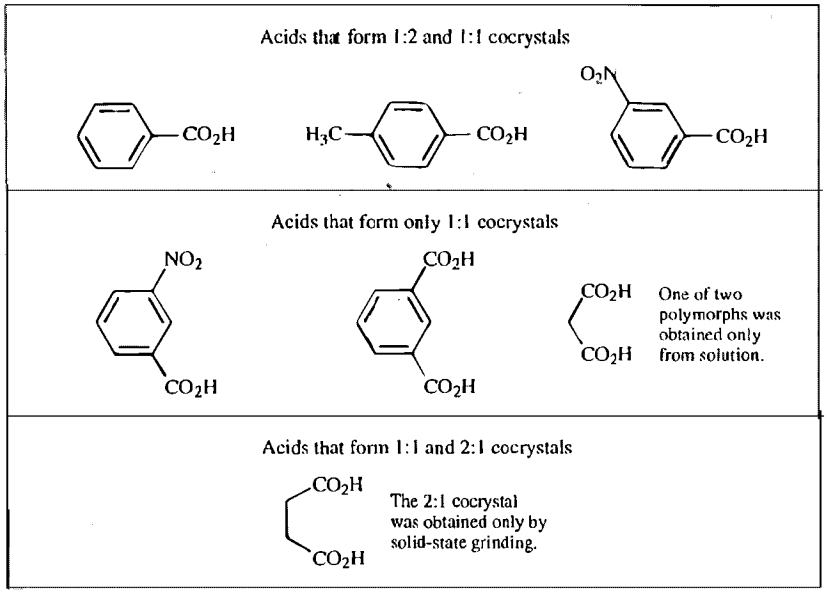


Figure 1.7 Observed stoichiometries of cocrystals of 2-aminopyridine with the compounds listed here (Etter and Adsmond, 1990).

Polymorphs — When two crystals have the *same chemical composition* but *different internal structure* (molecular packing) they are polymorphic modifications, or polymorphs. (Think of the three forms of carbon: diamond, graphite, and fullerenes.)

Solvates — These crystal forms, in addition to containing molecules of the same given substance, also contain *molecules of solvent* regularly incorporated into a unique structure. (Think of wet, setting plaster: $CaSO_4 + 2\,H_2O \rightarrow CaSO_4{\cdot}2H_2O$)

Habits — Crystals are said to have different habits when samples have the *same* chemical composition and the *same* crystal structure (*i.e.*, the same polymorph and unit cell) but display different shapes. (Think of snowflakes.)

Together, these solid-state modifications of a compound are referred to as **crystalline forms**. When differences between early batches of a substance are found by microscopic examination, for example, a reference to "form" is particularly useful in the absence of information that allows the more accurate description of a given variant batch (*i.e.*, polymorph, solvate, habit, or amorphous material). The term **pseudopolymorphism** is applied frequently to designate solvates.

To put these important definitions into a practical context, let us look at two cases in which a drug was crystallized from several different solvents and different-shaped crystals resulted in each experiment. (See Figures 1.8 and 1.9.)

Although sometimes dramatically different shapes were obtained upon changing solvents for the various crystallizations, the final interpretations in the two cases were significantly different. Figures 1.8 and 1.9 can be used to illustrate the application of the terminology defined in the previous paragraphs. Upon first seeing these pictures, it might be asked: "Although each of these drugs shows different *morphology* with different treatment, are the different-shaped crystals *polymorphs*, *solvates* or merely different *habits*?" After various investigations (*cf.* Methods, Chapter 2) it was concluded that all *forms* of the aspirin (Figure 1.8) have the same *structure* and therefore each is a different *habit* of the aspirin crystal. The various crystals of β-estradiol, however, were found to exist as a number of *solvate* forms (two *unsolvated* forms are also known but not shown in Figure 1.9). At this point we are aware that: (a given structure can form crystals of quite different shapes; and a given drug may exist in more than one crystal structure or crystal form (*i.e.*, polymorph or solvate).)

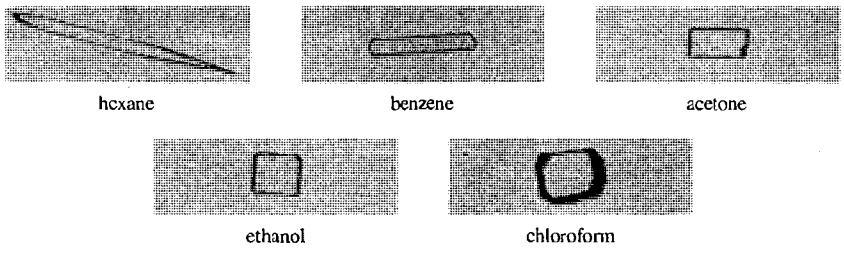


Figure 1.8 Aspirin crystals grown from different solvents.

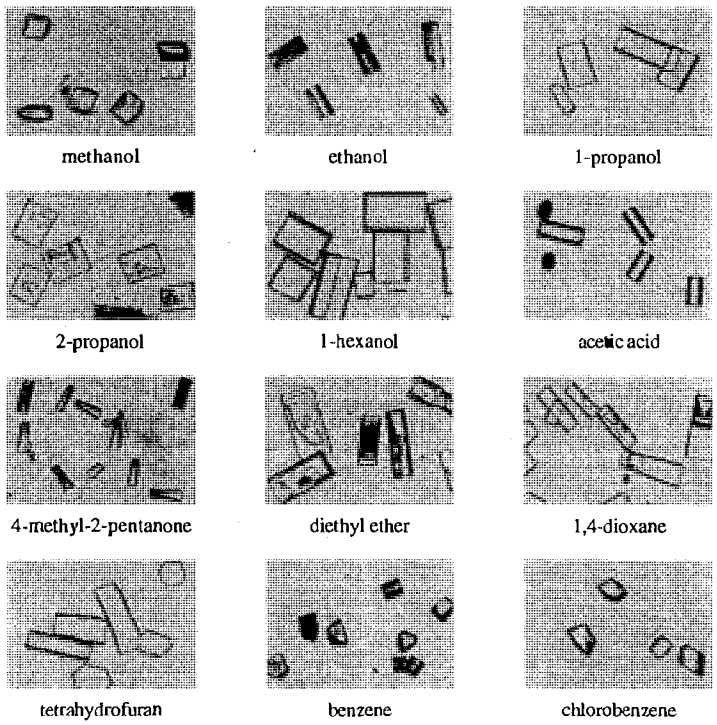


Figure 1.9 β-Estradiol pseudopolymorph crystals (solvate and crystallizing solvent are indicated, Kuhnert-Brandstätter, 1971).

1.4 PROPERTIES THAT AFFECT PHARMACEUTICAL BEHAVIOR

The familiar example of pure carbon in its three forms—diamond (tetrahedral lattice), graphite (polyaromatic sheets), and fullerenes (polyaromatic spheres)—dramatizes the profound effect that differences in crystal structure can have on the properties of a solid. Similar effects can apply to other solid compounds, including drugs. The complex nature of manufacturing operations and regulatory requirements peculiar to the pharmaceutical industry thus demands an even closer look at how the properties of a given drug can vary with each of its solid-state forms. Given the endless chemical variety of modern drug molecules it becomes obvious why solid-state studies are vital to the thorough characterization of pharmaceuticals.

Many physicochemical properties of a drug (see Table 1.3) vary when the solid-state *structure* of the substance is altered. The *practical significance* of any of these differences will, of course, vary from case to case.

Other properties of drug crystals that are of concern primarily in pharmaceutical *operations* also need to be addressed. These are properties that vary even when the crystal structure is fixed and are directly or indirectly related to surface relationships and thus largely controlled by **crystal habit** and **size distribution** (see Table 1.4). These

Table 1.3 Properties of a Compound that Depend on Structure Differences

Density	Water Uptake	Solid-State Reactivity
Hardness	Optical Properties	Physical Stability
Cleavage	Electrical Properties	Chemical Stability
Solubility	Thermoanalytical Behavior	

Table 1.4 Some Areas Where Control of Solid Form and Size Distribution are Important

Yield	Milling	Dissolution
Filtration	Mixing	Suspension Formulation
Washing	Tableting	Lyophilization
Drying	Flowability	

variables determine how particles behave with respect to neighboring particles (and upon exposure to solvent or solvent vapor) and thus the physical properties of powders.

At this point, the concept that these crystal properties are directional is introduced. In discussing symmetry and space groups (see Sec. 1.2A), it is important to convey the notion that unit cells contain different symmetry elements along their axes. A necessary consequence of this fact is that *most drug crystals have different properties in different directions*, or alternatively stated, *the chemistry on the different faces of a drug crystal may be quite different*. Both the structure and the properties, in short, are **anisotropic**. For example, one face of a crystal may be studded with carboxyl groups whereas another face might be entirely occupied by phenyl moieties, thus giving rise to some relatively hydrophilic surfaces and some hydrophobic surfaces, to mention only one consequence. Furthermore, with a change in crystal habit, the relative areas, hence the relative chemical importance of these two kinds of faces would be altered. If we now consider additional crystal forms of the same compound, the anisotropic chemical variability must be regarded anew for each polymorph and solvate.

Although it is by now obvious that control of crystal formation is of extreme importance, this control is not always easy to achieve. What general principles dictate the formation of crystals?

1.5 How Crystals Form

In this section we discuss how crystals form and the factors that influence crystallization. Table 1.5 lists the common crystallization methods employed for pharmaceuticals. Most of the methods covered in Table 1.5 depend on reducing the **solubility** of the compound by one means or another. It is therefore necessary to carefully define the solubility-related terms that will be used repeatedly in the discussions that follow.

A. Solubility

The solubility of a solid substance is the concentration at which the solution phase is *in equilibrium with a given solid phase at a stated temperature and pressure*. Under these conditions the solid is neither dissolving nor continuing to crystallize. Note that the definition implies the presence of a specific solid phase. Once determined under the

Table 1.5 Common Methods for the Production of Solids in the Pharmaceutical Industry

Evaporation (including spray drying and slurry fill)
Cooling a solution
Seeding a supersaturated solution with crystals of the desired form
Freeze drying (including from mixed solvents)
Addition of antisolvents
Salting out
Changing pH
Addition of reagent to produce a salt or new compound
Deliberate phase transitions during slurry, washing or drying steps
Simultaneous addition of two solutions

stated conditions, however, we can talk about the "solubility" of a given phase (*e.g.*, a specific polymorph or pseudopolymorph) as a quantity, even in the absence of that solid phase.

Use of the term "equilibrium" in connection with crystallizing systems requires clarification. When a substance exists in more than one crystal form, that is, when other polymorphs are possible, only the *least soluble* of these at a *given* temperature is considered the most physically stable form at that temperature, all others are considered to be **metastable forms.** In given cases, a solution of a substance may be in apparent equilibrium with one of these metastable phases for a long time, in which case, the system is in metastable equilibrium and is expressing the thermodynamic solubility of *that* solid form.

It is important to stress the difference between polymorphs and solvates (pseudopolymorphs) at this point. If a pseudopolymorph exists, it is always (with few exceptions) the most stable form in the solvent that produces the pseudopolymorph.

Undersaturation pertains to solutions at a lower concentration than the saturation value (*i.e.*, diluted solutions). *Crystals will dissolve in undersaturated solutions.*

Saturation is the state of a system where *the solid is in equilibrium with the solution*, or in other words, *the solution will neither dissolve crystals nor let them grow* (*i.e.*, the concentration of the solution represents the solubility value for that crystalline phase).

Supersaturation pertains to solutions that, for one reason or another (*e.g.*, rapid cooling of a saturated solution without forming crystals) are at a higher concentration than the saturation value. *Supersaturation is required for crystals to grow.*

B. Nucleation

Supersaturated solutions can sometimes remain in that condition for long periods without forming crystals. For example, the reader may have heard of slowly cooling very clean water to well below its freezing point of 0 °C without the formation of ice crystals taking place. The first step in forming crystals from a supersaturated solution requires the assembly of a critical number of ordered molecules (unit cells) into viable **nuclei.** This process is termed **primary nucleation.** Assemblies below the critical number tend to dissolve while those above the critical number persist and grow into recognizable crystals. This behavior is based on the simple fact that the surface area of a spherical body increases with the square of its radius but the volume increases with the cube

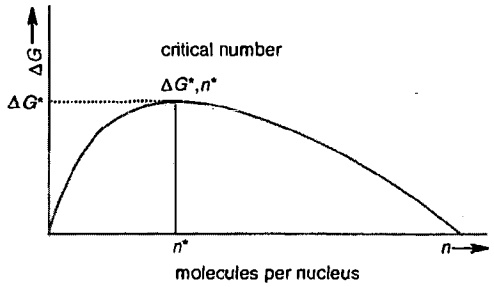


Figure 1.10 Free energy changes (ΔG) which occur during nucleation. Molecules assemble and disassemble until a nucleus of a critical number with an energy ΔG^* is achieved; then crystallization ensues as the size of the nucleus increases (Lieser, 1969).

of the radius. In other words, as an assembly becomes larger, the internal bonds holding it together become relatively more significant than the surface forces (solvent-solute interactions) acting to pull the particle apart. A more formal explanation of this phenomenon is given in Figure 1.10.

Despite various tidy theoretical analyses of nucleus formation that have been derived, nucleation in the laboratory or industrial setting remains very difficult to control in perhaps the majority of cases, due to the many disparate factors that are observed to affect nucleation (Table 1.6). In addition to primary nucleation, there is a phenomenon known as **secondary nucleation** which involves further crystallization after initial crystals are formed (either from deliberate seeding or primary nucleation). Among the factors which affect secondary nucleation are: agitation (including the design and type of crystallization vessel and agitator); temperature and concentration gradients; friable (breakable) crystal form or habit; and crystal irregularities caused by impurities. Secondary nucleation sometimes has undesirable consequences since it tends to produce excessive numbers of very small particles. Furthermore, once crystallization begins, factors like concentration, supersaturation, and many of the parameters in Table 1.6 may change, producing a dynamic environment that makes continued control of the process exceedingly difficult.

The most important lesson in this discussion is that *the number of particles and the crystal form resulting from a crystallization procedure are determined by nucleation*

Table 1.6 Factors that may Initiate Nucleation

Pre-existing nuclei on equipment or in air
Foreign particles of a suitable nature
Deliberate seeding with desired phase
Local hypersaturation by soluble metastable phase
Separation of a liquid phase during processing (*e.g.*, a temperature change or addition of antisolvent)
Local hypersaturation at an immiscible solvent interface
Ultrasonic or shock waves
Scratched surfaces
Local temperature irregularities
Local concentration gradients (*e.g.*, created by surface evaporation or reagent addition)

events. Thus: "one nucleus, one large crystal; a billion nuclei, a billion tiny crystals." In polymorphic systems nuclei of different structures can form and coexist in a given crystallization, in which case a mixture of crystal forms may be found in the final product when kinetic factors prevent achievement of equilibrium.

Consider the situations shown in Figure 1.11. In the top two panels, a crystallization procedure, using apparently the same protocol, affords different polymorphs on separate occasions (needles and plates). In the bottom panel, the "same procedure" results in a mixture of the polymorphs. In these cases, lack of control of the nucleation process leads to lack of control of the polymorphs present. It is therefore common practice to add nuclei of the desired phase deliberately at an appropriate stage in an industrial crystallization. This process is called **seeding**, and is one of many measures used to control the outcome of crystallizations.

C. Transitions Between Crystal Forms

When different crystal forms are possible for a substance each form has a solubility value under a fixed set of conditions: solvent composition; temperature; and pressure. Even if crystals of two forms have been produced, however, the system will always

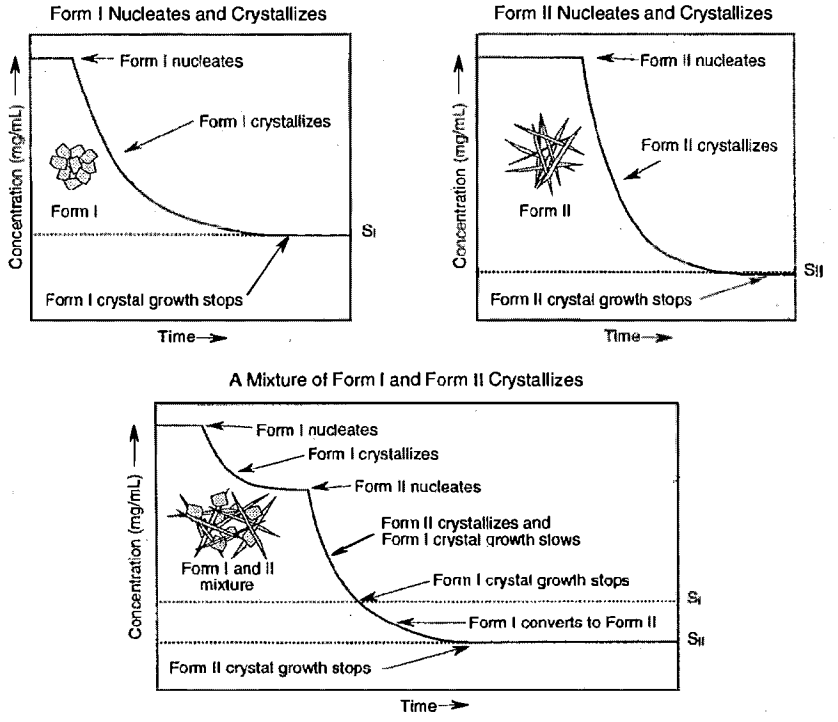


Figure 1.11 Uncontrolled crystallization in a polymorphic system showing the different polymorphs (top panels) or the mixture of polymorphs (bottom panel) which can result. (SI and SII are the solubility limits for Forms I and II, respectively.)

tend to produce only the less soluble of two forms eventually (see Figure 1.11). To be sure, the time it takes to express this tendency depends on kinetic factors and may be quite variable; but in any event, a less soluble form never converts to the more soluble form under rigorously defined conditions.

A few illustrations of the dissolution behavior of some polymorphic drugs may help to review these relationships as they apply to solutions at constant temperature. Figure 1.12 shows concentration versus time plots for furosemide and Figure 1.13 shows the concentration versus time plots for theophylline. In Figure 1.12 there is no conversion to the most stable crystal form during the experiment. In contrast, in Figure 1.13 the less stable anhydrate converts to the hydrate during the experiment providing unequivocal proof that the hydrate is more stable (less soluble) than the anhydrate. In these examples it is obvious which form of theophylline is the less soluble. Under

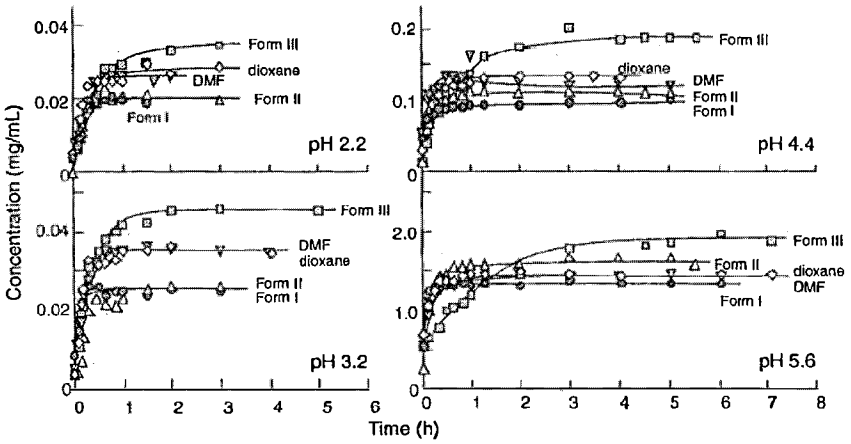


Figure 1.12 Dissolution profiles of the different crystal forms of furosemide in buffer solution at various pH values at 37° C (Matsuda and Tatsumi, 1990).

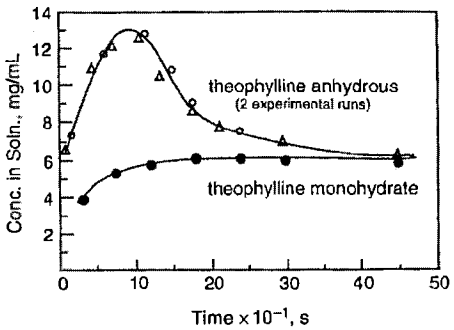


Figure 1.13 Concentration versus time curves for anhydrous and hydrated crystal forms of theophylline in water at 25 °C (Shefter and Higuchi, 1963).

these conditions, this form will never convert to the other, and can therefore also be referred to as the thermodynamically more **stable form**.

When temperature is introduced as a variable, however, further distinctions concerning the relative stability of alternative forms need to be made. The thermodynamic activity (usually observed as solubility) of each form may change quite differently as a function of temperature. **Monotropic** systems are defined as systems where a single form is always more stable regardless of the temperature. **Enantiotropic** systems are defined as systems where the relative stability of the two forms inverts at some transition temperature. These relationships are evident in graphic form (see Figure 1.14).

In actual practice, it is customary to plot log solubility versus $1/T$ for each solid phase (*i.e.*, as a so-called **van't Hoff plot**). These plots give, in most cases, the data in a linear form that lends itself to extrapolation, so that transition points can be determined even when complete data for a given solid phase are unreliable or unavailable. Figure 1.15 shows a van't Hoff plot of solubility versus $1/T$. In this case, there is a transition point where the lines cross and the relative stabilities of the two forms are the same ($\Delta G = 0$). Extrapolation of data 10 K beyond the experimental range is prone to produce large errors and is not reliable.

Transitions from one solid phase to another can occur in the absence of solvent. The mechanisms and kinetics of such solid-state transitions can be very complex and are addressed in Chapters 14, 15 and 20. For example, Kitaigorodskii *et al.* (1965) showed that a pin-prick can initiate the solid-state transformation of α-*p*-dichlorobenzene to β-*p*-dichlorobenzene within a single crystal. The transformation of α- to β-*p*-dichlorobenzene is delineated by the spread of the reaction front from the nucleation site through the crystal. A related process is the thermally-induced rearrangement of the α- to β form of *p*-nitrophenol (Coppens and Schmidt, 1965). In this reaction, needle-shaped single crystals rearrange with the phase boundary moving approximately perpendicular to the needle axis. Grinding or other input of mechanical energy induces the polymorphic transformation of chlorpropamide (Otsuka *et al.*, 1989), fostedil (Takahashi *et al.*, 1985), chloramphenicol palmitate (Kaneniwa and Otsuka, 1985), and several other drugs (Chan and Doelker, 1985).

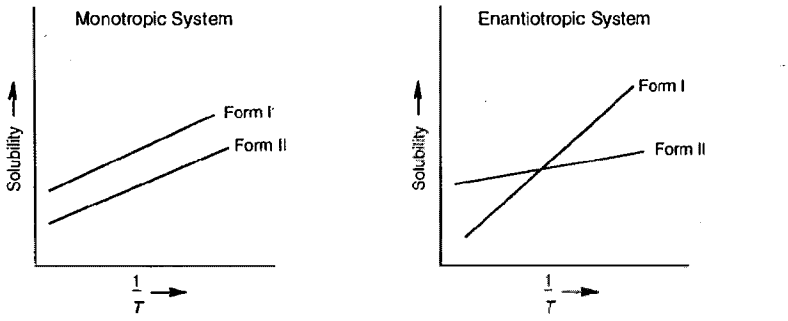


Figure 1.14 Schematic graphs of concentration versus temperature for a monotropic system and an enantiotropic system.

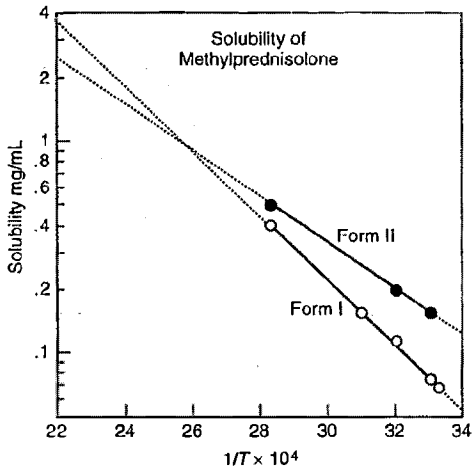


Figure 1.15 A van't Hoff plot of the water solubility of two methylprednisolone crystal forms (log of the solubility as an inverse function of temperature, Higuchi *et al.*, 1963).

D. Other Spontaneous Changes in the Solid State

In addition to the crystal-to-crystal transitions treated above, we should mention another change that can affect properties of drugs: **crystal ripening**. Crystal ripening occurs when the crystal size increases as the solid remains in contact with solution. In this process, larger crystals grow (or ripen) at the expense of smaller crystals. In practice, newly formed crystals contain many "high-energy sites" from the inclusion of impurities, disordered areas (due to rapid growth), and other causes. Crystals less than about one micrometer in size also have excess free energy because of their high surface curvature. These "high-energy" crystals tend to dissolve and then contribute to the ripening process when the material is redeposited on a larger crystal, that is, on a lower free energy site. This process is called "**Ostwald ripening**," after its discoverer (Ostwald, 1896). The effect of ripening on crystal size is shown in Figure 1.16. Control of this process is important in cases where small particle sizes are needed (*e.g.*, aerosol prod-

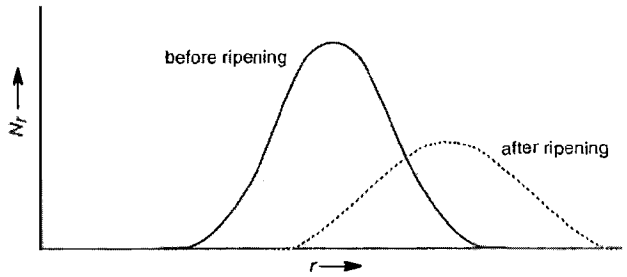


Figure 1.16 Change in crystal size distribution as a result of ripening (Lieser, 1969).

ucts). In addition, ripening can explain particle size changes that take place in suspension during crystallization or wet granulation.

1.6 PROPERTIES OF AMORPHOUS SOLIDS

Amorphous solids have no long-range order, are not crystalline, and therefore do not give a definitive **X-ray diffraction pattern**. The properties of these solids are of interest because they differ considerably from those of their crystalline counterparts. Amorphous solids do not exhibit **birefringence** under crossed polars on the microscope. The most profoundly amorphous solid is a glass in which the atoms and molecules exist in a totally non-uniform array. Amorphous solids have no faces and cannot be identified as either habits or polymorphs. Because the properties of amorphous solids are *direction independent* these solids are called **isotropic**.

Amorphous forms can be prepared by rapid cooling (Fukuoka *et al.*, 1991), grinding (Kitamura *et al.*, 1989; Otsuka and Kaneniwa, 1990), or by lyophilization and spray drying (Haleblian *et al.*, 1971; Pikal, 1990). For example, rapid cooling gives an amorphous form of chloramphenicol palmitate (Kimura and Hashimoto, 1960), as did over 20 other pharmaceuticals (Fukuoka *et al.*, 1991 and references therein). Lyophilization gave amorphous forms of fluprednisolone (Haleblian *et al.*, 1971), antibiotics (Pikal *et al.*, 1977), and proteins (Pikal, 1990).

An amorphous solid is characterized by a unique **glass transition temperature** T_g, the temperature at which it changes from a **glass** to a **rubber**. When T rises above T_g, the rigid solid can flow and the corresponding increase in molecular mobility can result in crystallization or increased chemical reactivity of the solid.

Although amorphous solids often have desirable pharmaceutical properties, such as rapid dissolution rates (Fukuoka *et al.*, 1987), they are not usually marketed because of their lower chemical stability (Pikal *et al.*, 1977) and their tendency to crystallize (Fukuoka *et al.*, 1991), thus overriding any adventitious properties. Nevertheless, in some cases, amorphous forms are used as products. An excellent example is novobiocin (Mullins and Macek, 1960) which exists in a crystalline and an amorphous form. The crystalline form is poorly absorbed and does not provide therapeutic blood levels; in contrast, the amorphous form is readily absorbed and is therapeutically active. Further studies show that the solubility rate of the amorphous form is 70 times greater than the crystalline form in 0.1 N HCl at 25 °C when particles <10 μm are used. Table 1.7 (Haleblian, 1975) shows data for the plasma levels of novobiocin's amorphous and crystalline forms and for sodium novobiocin, which also gives detectable plasma levels, but is chemically unstable in solution. Unless special precautions are taken, an amorphous form will sometimes be slowly converted to the crystalline form (Fukuoka *et al.*, 1991 and references therein).

Table 1.7 Dog Plasma Levels of Novobiocin after Administration of Different Novobiocin Forms

	Hours after dose (mg/mL)						
Form	0.5	1.0	2.0	3.0	4.0	5.0	6.0
Sodium novobiocin	0.5	0.5	14.6	22.2	16.9	10.4	6.4
Amorphous novobiocin acid	5.0	40.6	29.3	22.3	23.7	20.2	17.5
Crystalline novobiocin acid	Not detectable at any time						

Haleblian, 1975.

1.7 MOISTURE UPTAKE BY SOLIDS

Some crystalline solids take up water from the atmosphere and are termed **hygroscopic solids** in the literature. Unfortunately, there can be no clear definition of hygroscopic solids because **hygroscopicity** is a relative term. Hygroscopicity is determined by both a kinetic and a thermodynamic term and is a function of the atmospheric relative humidity. In high relative humidities, many solids are hygroscopic. In atmospheres of low humidity, only a few solids will be hygroscopic. Another factor influencing hygroscopicity is surface area and thus porosity. The larger the surface area of the solid, the more rapid the uptake of moisture. This is because solids with larger surface areas have more sites for adsorption of water molecules. Zografi *et al.* (1991) suggested that hydroscopicity not be used and that the relative humidity at which a water-soluble solid **deliquesces** (RH_0) should be used instead. This is a scientific term that can be clearly defined and will not vary from investigator to investigator but is only applicable for highly water soluble solids.

Zografi *et al.* (1991) also described guidelines for the establishment of pharmaceutical compendium water specifications and processes by which water is adsorbed by solids. They suggested that surface water generally does not amount to more than 1 to 3 molecular layers. Since the cross-sectional area of a water molecule is about 0.125 nm^2, 1 to 3 molecular layers would amount to only negligible percentages of water. Table 1.8 shows the calculated layers of water on the surface of a solid as a function of surface area and particle diameter. It is clear from this table that even for the smallest particles, 0.1% water will form a monolayer on the surface. Hence, three layers would only account for about 0.3% water. Obviously, claims for large increases in weight because of surface moisture are not consistent with this observation.

When solids that are not solvates contain large amounts of water, it has been hypothesized that water must be taken up into the solid by disordered or high-energy regions such as defects and amorphous sites. They further suggested that such effects might be exaggerated by manufacturing processes that reduce particle size, such as micronization, milling, or related processes known to increase the number of high energy sites. Of course, some solids can take up so much water during these processes that they become damp or even liquefy at RH_0 (Zografi *et al.*, 1991). This tendency is usually easily detected by microscopic observation. The mass of water necessary for the solid to change from a glass to a more fluid-like system is designated W_g.

The formation of crystal hydrates, of course, is another way for water to be incorporated into a solid. In these cases the water molecules generally occupy a specific crystallographic site in the solid. This site can be determined by X-ray crystallography which thus unequivocally proves the existence and composition of the hydrate. How-

Table 1.8 Calculation of the Number of Molecular Layers of Water on Solid Spheres of Sucrose as a Function of the Surface Area and Particle Diameter.[a]

Number of Layers	Specific Surface Area (m^2/g)	Particle diameter (microns)
1.1	3.8	1
11	0.38	10
42	0.10	38
110	0.038	100

[a] Density = 1.59 g/cm^3 at 0.1% water content.

ever, many hydrates exist in which the water is located in tunnels within the crystal. The water can be located accurately only by determination of the crystal structure at low temperatures (if even then). In these cases, the water content may change rather easily with changes in relative humidity.

Plots of vapor pressure versus relative humidity are an excellent way to determine the nature of a solid with respect to water sorption (see Figure 1.17). The different kinds of behavior that these plots may be expected to show include:

1. Virtually no water uptake
2. Gradual water uptake, characteristic of an amorphous material or a **nonstoichiometric hydrate** (a hydrate without a simple ratio of water to host molecule)
3. "Stair-step" water uptake, characteristic of a stoichiometric hydrate

Figure 1.18 shows the behavior of two stoichiometric hydrates (a monohydrate and a sesquihydrate) as well as a nonstoichiometric hydrate of sodium cefazolin. In addition, amorphous sodium cefazolin also exists and takes up and loses water in a more or less gradual fashion as described below.

Sorption of water into amorphous solids or regions of a solid involves dispersion or dissolution of the water molecules within a solid. The more polar a solid, the greater the amount of water taken up. Obviously, in such systems the water content depends upon relative humidity. In addition, the amount of water absorbed may not reach equilibrium for several months (Zografi *et al.*, 1991).

In summary, Zografi *et al.* (1991) made the following recommendations with regard to water specifications:

1. A complete profile of relative humidity versus water content (weight) should be reported for all reference standards.
2. For amorphous solids, both T_g and W_g should be reported.
3. For deliquescent solids, the RH_0 and an appropriate warning on the label should be provided.
4. For stoichiometric hydrates, the water specifications should reflect the stoichiometry.
5. Attention should be paid to materials which do not form well-defined hydrates and can take up or lose water as the humidity is

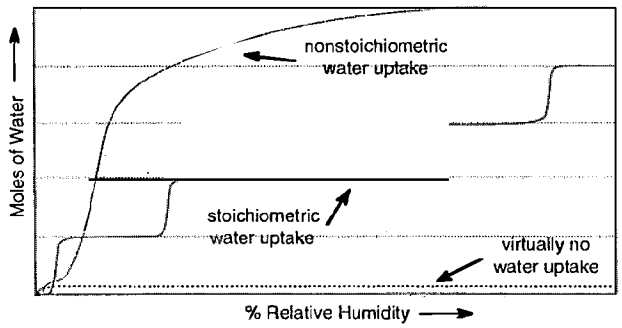


Figure 1.17 Idealized vapor pressure versus relative humidity plot.

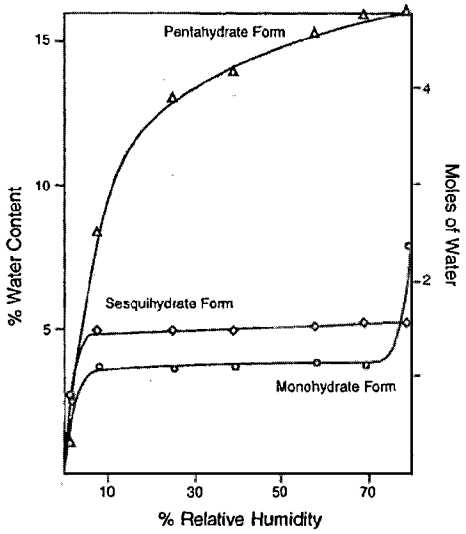


Figure 1.18 Vapor pressure versus relative humidity diagrams for three hydrates of sodium cefazolin. The sesquihydrate and monohydrate behave normally and the "pentahydrate" is actually a nonstoichiometric hydrate (Osawa *et al.*, 1988; Pfeiffer, 1988).

varied. Any structural changes that accompany changes in water content should be noted. (Some hydrates can lose water without changing crystal structure. This is due to the formation of an extremely stable crystal packing network by the host molecule.)

1.8 LYOPHILIZED POWDERS

Many antibiotics, proteins, and other drugs are marketed as lyophilized powders. The process of freezing a solution of the drug and then removing the ice by sublimation yields a product that is low in moisture and high in specific surface area. Although the solid may crystallize during the freeze drying process, the usual product is an amorphous powder. If the solid crystallizes during storage, a slower dissolution rate would be expected.

1.9 PATENTS ON VARIOUS CRYSTAL FORMS

A review of the patent literature indicates that crystal forms and processes involving crystal forms are patentable. Of the approximately 41,000 patents in the *Pharmaceuticals* section of *Chemical Abstracts* (listed prior to August 28, 1991), 122 use the keyword "crystal," 10 use the keyword "polymorph," 27 use the keyword "solvate," and 191 use the keyword "hydrate," or keywords involving higher hydrates. In addition, 79 use the keyword "crystallization." Many of the most interesting patents which were retrieved in this search are listed in Table 1.9. It is important to note that this search is

Table 1.9 Selected Patents on Various Crystal Forms Listed in Chemical Abstracts

Substance	Crystal Form	Utility	Abstract No.
Sodium Acetylsalicylate	crystalline	stable	**108**:44030*n*
Amoxicillin	anhydrous sodium salt	nonhygroscopic and stable	**102**:172646*f*
Amoxicillin	pyrrolidone solvate	injectable	**96**:74631*k*
Amphotericin B	crystals	purification process	**112**:240473*f*
Azetidine Sulfonic Acid	crystalline anhydrous form	improved stability	**99**:10852*n*
Azithromycin	dihydrate	nonhygroscopic	**111**:45265*s*
Beclomethasone	chlorofluorocarbon solvate	stability	**94**:52972*d*
Beclomethasone	solvates	aerosol formulation	**96**:91650*h*
Beclomethasone Dipropionate	Freon® solvate	aerosols	**113**:29296*p*
Beclomethasone Diproprionate	alkane solvates	formulation	**102**:209431*k*
Beclomethasone Diproprionate	new crystal form	does not form solvates with propellants	**94**:162747*s*
Benzimidazole Derivative	crystalline	thermostable with small particle size	**108**:137876*h*
Buspirone·HCl	interconversion	preparation of either form	**111**:239476*g*
Catechin	monohydrate and anhydrate	formulations	**103**:59298*b*
Cefadroxyl	anhydrate	preparation	**111**:239478*j*
Cefadroxyl Monohydrate	monohydrate	preparation	**111**:239477*h*
Cefahydroxyl Monohydrate	crystalline	preparation from CH_3CN solvate	**103**:166151*v*
Cefamandole Derivative	γ-form	stability and lack of hygroscopicity	**86**:78672*r*
Sodium Cefazolin	monohydrate	crystallization process	**90**:61247*r*
Ceftazidime	anhydrous crystal modification	stability	**102**:67395*a*
Ceftazidime Intermediate	crystalline $HCl·H_2O$	purification	**102**:191162*m*
Ceftazidime·$5H_2O$	pentahydrate	increased activity	**105**:30045*x*
Cefuroxime	crystalline sodium salt	crystallization	**102**:32299*v*
Cephalexin	crystalline	formulation	**84**:184895*j*
Cephalexin	monohydrate	stability	**74**:6404*j*
Cephalexin	*t*-type monohydrate	novel	**89**:169093*f*

Table 1.9 (continued) Selected Patents on Various Crystal Forms Listed in Chemical Abstracts

Substance	Crystal Form	Utility	Abstract No.
Cephalexin·HCl	monohydrate	immediate release	**103**:129047*v*
Cephalosporin Antibiotic	heptahydrate sodium salt	improved stability	**100**:73975*q*
Sodium Cephalothin	crystallization	improved filtration properties	**87**:141273*z*
A Cephem Carboxylic Acid	hydrates	stability	**110**:29096*m*
Sodium Cephem-carboxylate	crystals	formulation	**103**:129069*d*
Cephradine	hydrate	stability	**115**:35741*n*
Cimetidine	Form A	formulation	**100**:12669*w*
Cimetidine	Form B	formulation	**109**:237026*v*
Cimetidine	Form B	preparation	**109**:176349*d*
Cimetidine	Form Z	formulation	**99**:10848*r*
Corticosteroids	chlorofluorocarbon solvates	lack of crystal growth in aerosols	**85**:51743*g*
Cyclosporin	orthorhombic form	sustained release	**112**:145575*g*
DDI, DDT	monohydrate	high water solubility	**115**:35706*e*
Deoxycholic Acid	unsolvated crystals	improved formulations	**94**:162743*n*
Deoxyspergalin	crystalline	improved hygroscopicity, stability, handling	**115**:15582*h*
Dianemycin glycon	crystalline anhydrous form		**106**:23267*p*
Dibenzopyrone	polycrystalline form	improved blood levels	**86**:95990*k*
Famotidine	morphologically homogeneous	homogeneous forms	**108**:192770*u*
Famotidine	separation of crystal forms	increased activity	**111**:180678*u*
Flunisolide	crystal form	aerosols	**93**:138020*h*
Flunisolide	crystal form	aerosols	**94**:214609*v*
Gabapentin Monohydrate	monohydrate	novel crystal form	**113**:138572w
Gabexate Mesylate	lyophilized crystals	high stability	**111**:63927*p*
Ibuprofen	crystalline	improved flow properties	**102**:50901*q*
Inotropic Agent	hydrates	administration	**112**:204687*v*
Insulin	crystalline suspension	improved release	**94**:214619y

Table 1.9 (continued) Selected Patents on Various Crystal Forms Listed in Chemical Abstracts

Substance	Crystal Form	Utility	Abstract No.
Isoglutamine Derivative	monohydrate	more stable, less hygroscopic	**106**:125878*f*
Josamycin	solvent-free crystals	formulation	**87**:90714*j*
LY163892	dihydrate and trihydrate	preparation and formulation	**114**:88656*z*
LY163892	solvates	intermediates	**114**:88639*w*
LY163892 (antibiotic)	monohydrate	formulation	**111**:201646*z*
Meclophenoxate·HCl	type I crystals	more stable, less hygroscopic	**107**:64843*n*
Mefloquine·HCl	polymorph	improved solubility and bioavailability	**103**:129044*s*
Methylbutylamine·HCl Derivative	monohydrate	not hygroscopic	**107**:223314*j*
Methyldopa Salts	crystalline solvates	crystalline	**107**:242598*w*
Milrinone	3 crystal modifications	formulations	**110**:63770*m*
Naphthyridine Carboxylic Acid	sesquihydrate	stability	**98**:59888*x*
Necromodil Na	Form B	stability	**108**:226832*h*
4-Oxo-2-azetidinyl Derivative	crystals	crystalline	**108**:137873*e*
Penicillin Derivative	hemisolvate	stability	**85**:130523*p*
Phenylpropiophenone	spherical crystals	sustained release	**115**:15598*t*
A piperazine·HCl	new crystal form	increased solubility	**105**:158806*p*
Piroxicam	β-form	improved flow properties	**111**:140479*y*
Prazosin·HCl	α-form	preparation	**99**:10849*s*
Pyran-9-one Derivative	polymorphs	particle size	**83**:152334*p*
N-Pyridylcarboxyamide	polymorphic monoethanolamine salt	increased stability	**105**:66460*t*
Quinolone Carboxylate	anhydrate	stability and preparation	**112**:185779*h*
Sorbitol	γ-form	improved tableting	**95**:30396*n*
Steroid	monoclinic or triclinic forms	preparation and formulation	**114**:214521*s*
Sulfametrole Hemihydrate	hemihydrate	no sediment upon storage	**107**:223316*m*
(*S*)-Timolol	hemihydrate	preparation	**114**:49576*d*

by no means comprehensive since several of the most important patents on crystal forms, including those on ranitidine hydrochloride and cefuroxime axetil, did not show up as "hits."

It is clear from Table 1.9 that patents based on solid-state properties have been issued for a wide range of drugs crystallizing in many different crystal forms and having many different uses. The types of drugs included in Table 1.9 range from antibiotics, to antiulcer drugs, to antitumor and antiviral agents, to anti-inflammatory agents. Proteins and various salts are also included. Polymorphs, solvates, hydrates of various types, and lyophilized crystals are among the crystal forms claimed. As might be expected, a wide range of uses is cited. Among the most frequent uses cited are improved formulation, handling, and stability. In addition, there are several patents on crystal forms with reduced hygroscopicity and improved solubility and bioavailability. Patents will no doubt continue to be issued on crystal forms. In fact, it is likely that the number of crystal forms patented will greatly increase since our ability to characterize and understand the crystal forms has greatly improved.

1.10 SOLID-STATE REACTIONS OF DRUGS

The scientific discipline of solid-state chemistry of drugs emphasizes studies of the chemical and physical properties of the various solid forms just discussed. These studies include solid-state phase transformations (polymorphic transformations), reactions in which solvent of crystallization is lost or gained, and a broad range of solid-state chemical reactions.

It is necessary to establish criteria for solid-state reactions in order to focus on true solid-state reactions. This will avoid a liquid-state reaction being identified as a solid-state reaction. Morawetz (1966) suggested four criteria for determining whether a reaction is a true solid-state reaction and a fifth and very important criterion can be added from Paul and Curtin (1973):

1. A reaction occurs in the solid when the liquid reaction does not occur or is much slower.
2. A reaction occurs in the solid when pronounced differences are found in the reactivity of closely related compounds.
3. A reaction occurs in the solid when different reaction products are formed in the liquid state.
4. A reaction occurs in the solid if the same reagent in different crystalline modifications has different reactivity or leads to different reaction products.
5. A reaction occurs in the solid phase if it occurs at a temperature below the eutectic point of a mixture of the starting material and products.

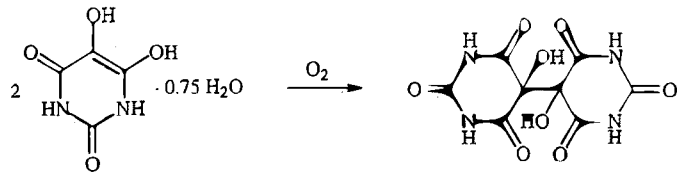
Once it has been established that the reaction is occurring in the solid state, the reaction can be understood in terms of a four-step process (Paul and Curtin, 1973):

1. loosening of the molecules at the reaction site
2. molecular change
3. solid solution formation
4. separation of the product phase

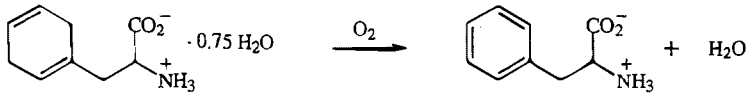
Table 1.10 Solid-State Chemical Reactions of Drugs

Solid-State Oxidations (Chapter 18)

Dialuric Acid (Clay *et al.*, 1982)



Dihydrophenylalanine (Ressler, 1972)



Phorbol Esters (Schmidt and Hecker, 1975)

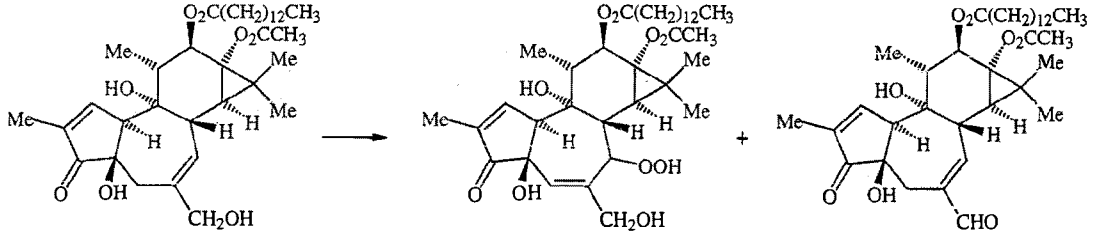
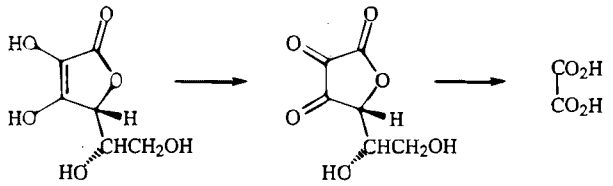
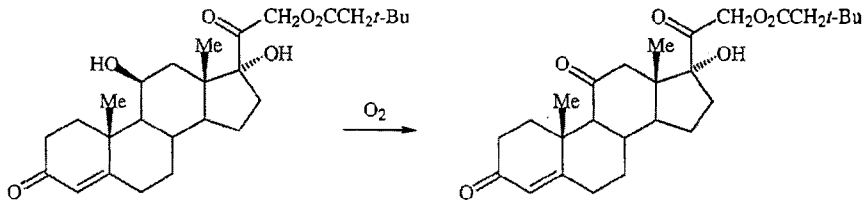


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Vitamin C (Rubin *et al.*, 1976)



Hydrocortisone *tert*-Butylacetate (Brenner *et al.*, 1969)



Vitamin D_2 (Kanzawa and Kotaku, 1953)

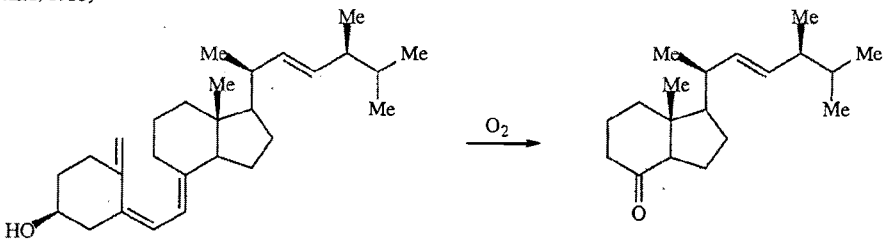
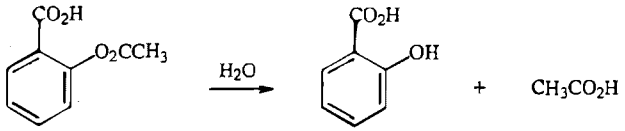


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Additions of Gases to Solids—Solid-State Hydrolyses (Chapter 19)

Aspirin (Leeson and Mattocks, 1958)



Nitrazepam (Genton and Kesselring, 1977)

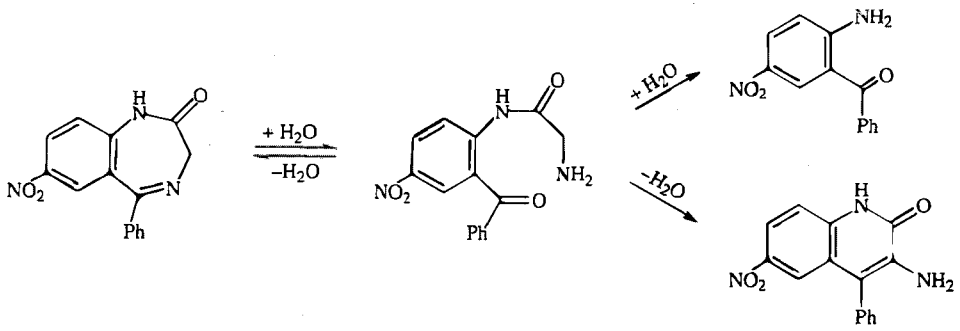
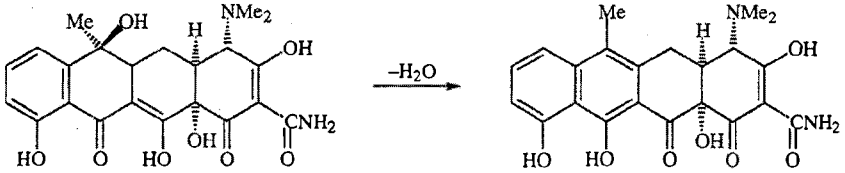


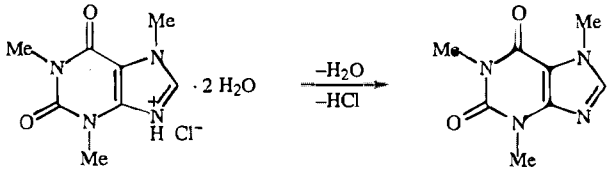
Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid-State Decomposition Reactions: A (solid) → B (solid) + C (gas) (Chapter 20)

Dehydration of Tetracyclines (Simmons *et al.*, 1966)



Dehydrochlorination of Caffeine Hydrochloride (Biedermann, 1883)



Decarboxylation of *p*-Aminosalicylic Acid (Lin *et al.*, 1978)

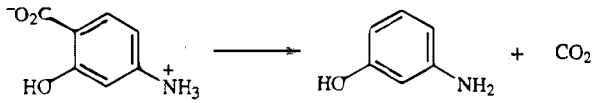
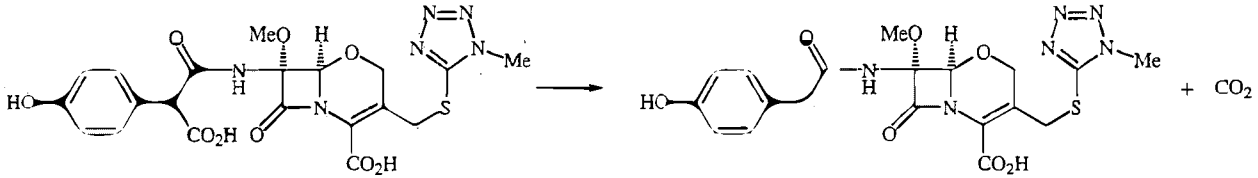


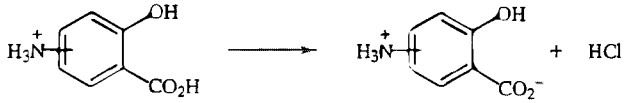
Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid-State Decomposition Reactions: A (solid) → B (solid) + C (gas) (continued)

Decarboxylation of Moxalactam (Pikal and Dellerman, 1989)



Dehydrochlorination of Aminosalicylic Acid Hydrochlorides (Lin *et al.*, 1978)



Solid-State Photochemical Reactions (Chapter 21)

Gibberellins (Adam and Voigt, 1971)

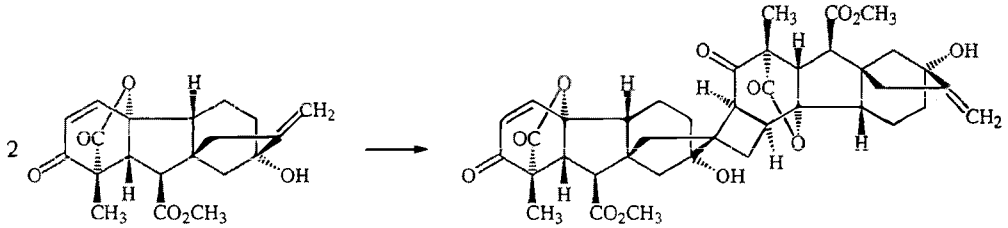
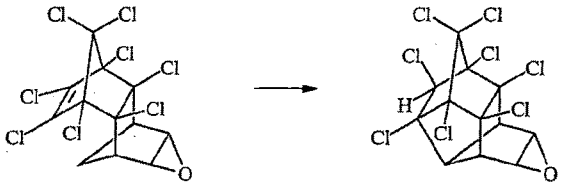


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Dieldrin (Benson, 1971)



Nifedipine (Hayase *et al.*, 1994)

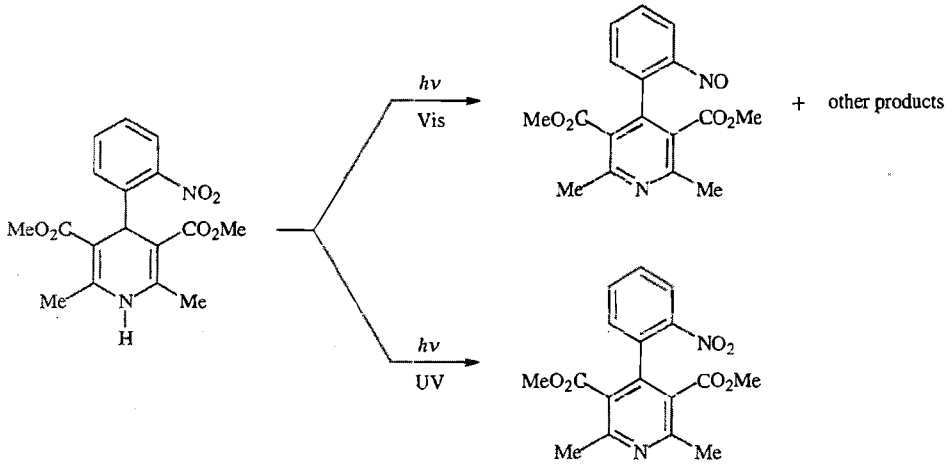
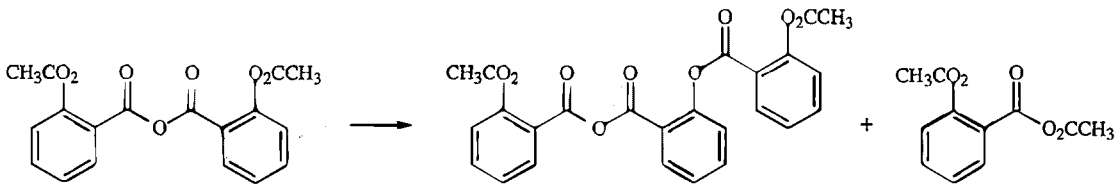


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid-State Thermal Reactions (Chapter 22)

Rearrangement of Aspirin Anhydride (Garrett *et al.*, 1959)

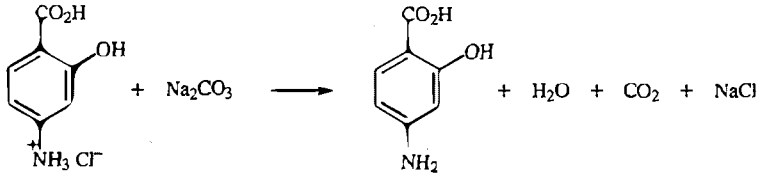


Rearrangement of a Triazenoimidazole (James *et al.*, 1969)

Rearrangement of the Methyl Ester of Tetraglycine (Sluyterman and Veenendaal, 1952)

Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid–Solid Reactions (Chapter 24)
Reaction of *p*-Aminosalicylic Acid Hydrochloride with Sodium Carbonate (Lin *et al.*, 1978)



These four steps are discussed in more detail in Part 5 of this book.

It is important to realize that many solid-state reactions of drugs involve drug degradations which have been studied mostly on the macroscopic level. In fact, few studies aimed at determining the molecular aspects of the solid-state chemistry of drugs have been published. These reactions are of interest because of a desire to prevent such degradation. Even for such common drugs as vitamin D_2 and vitamin A, the structures of only a few of the solid-state degradation products have been published. Therefore, in many respects, the solid-state chemistry of drugs is synonymous with drug degradation.

Table 1.10 summarizes some of the solid-state chemical reactions of drugs and is arranged according to the type of chemical reaction involved. Only solid-state reactions in which the chemical structure of the product(s) is known are included. The classification scheme used in this table is used throughout this book, and each class of reaction is treated in a separate chapter or chapters as noted in the table.

1.11 STABILITY TESTING

One of the practical areas encompassed by the field of solid-state chemistry of drugs is the area of stability testing. Stability tests are conducted on all marketed drugs in order to determine an expiration date after which the drug will not be sold. The FDA has issued guidelines for stability testing (*Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, 1987) and the draft of an update (*Guidance for Industry: Stability Testing of Drug Substances and Drug Products*, 1998). These guidelines describe the design and interpretation of stability studies, the content of stability reports, and methods for computing an expiration date.

Manufacturers are required to ensure that the drugs distributed and marketed are of the best possible quality. However, because the phrase "best possible quality" is vague, the government has attempted to define this idea in terms of current good manufacturing practices (cGMP).

Good manufacturing practices were published in the *Federal Register* on September 29, 1978. They require, among other things, that

1. essentially all products must bear an expiration date
2. all products bearing this date must describe the storage conditions under which this date applies
3. the stability-testing program must be defined in writing

An expiration date is required to assure that drug products have the identity, purity, structure, and quality described on the label and package insert during their period of use under the storage conditions described. If the product is subjected to higher temperatures than those described, then the actual expiration date will be sooner than the expiration date on the label.

Generally, stability studies and expiration dates should be determined under conditions approximating normal storage conditions rather than under accelerated conditions. One of the reasons is that elevated temperatures used in accelerated stability tests may be above the eutectic of the reactant or product and may result in misleading

information (see Figure 1.18). Nevertheless, a series of accelerated stability tests can be used to determine the best storage conditions.

For **accelerated stability tests**, each crystalline form and habit of the pure solid as well as solid-solid mixtures of the pure solid with **excipients** and **adjuncts** (additives used to prepare the pharmaceutical product) should be maintained at elevated temperature (different companies use different temperatures) in vials or ampoules. In addition, accelerated studies in which samples are deliberately exposed to light are often carried out. One ampoule or vial should be assayed each day using the most sensitive method available. The experiment should be run for at least two weeks, and the data should be used to determine the rate of decomposition. The rate is conveniently determined using the computer program described in Chapter 23. If the elevated temperature is too close to the melting point of the solid, liquid could form after only a few percent decomposition through the lowering of the melting point by the decomposition products present. Under these circumstances, it is probably best to lower the temperature and extend the study.

The activation energy is also of interest in predicting product stability. For determination of the activation energy, the kinetics (percentage of decomposition versus time) of the solid-state reactions are determined at three or more temperatures. However, the kinetics of solid-state reactions are often much more complicated than in the corresponding solution reactions. (Solid-state reactions are usually not clearly zero-order, first-order, etc., but are often of fractional orders.) Thus determination of the rate constant at different temperatures is difficult, if not impossible. In addition, because of the slowness of many solid-state reactions, rate studies are usually only carried through one or two half-lives. For this reason, (Carstensen (1974) suggests that first-order or zero-order kinetics should be assumed for determination of the activation energy. Thus the rates of decomposition are measured at several temperatures and plotted according to zero-order and first-order kinetics.) The equation that gives the best fit by statistical tests is then assumed to give the best rate constants. An attractive alternative approach is to apply the computer program discussed in Chapter 3 to the data.

(The rate constants (k) are then plotted versus temperature (T) according to the Arrhenius equation

$$k = Ae^{-E_a/RT} \tag{1.1}$$

where R is the gas constant. From this plot, A (the pre-exponential factor) and E_a (the activation energy) are determined and used to determine the rate constant (k) at the labeled storage conditions. This rate constant is then used to estimate the expiration date.)

(The reactivity of the compound in solution at elevated temperatures should also be determined to give information about the "intrinsic reactivity" of the drug.)

The stability of the drug in light is also usually determined. Each crystalline form and habit of the pure solid and mixtures with adjuncts and excipients is exposed in a suitable light cabinet under the following conditions: inert atmosphere, exposure to air, and exposure to increased humidity humidity. These latter studies can conveniently be performed using a glove bag. Samples are assayed each day using the most sensitive method available.

The container in which the drug has the greatest stability is selected. The best container is determined by measuring the rate of degradation of the drug in various

containers under various storage conditions. Obviously, the container and storage conditions in which the rate of decomposition is slowest should be chosen.

1.12 SUMMARY

This chapter summarizes the scope of the area of solid-state chemistry of drugs. It is clear that this is a broad, relatively unexplored area involving an understanding of crystallization, the properties of crystals, the forces holding crystals together, the properties of other solids (*i.e.*, amorphous solids), the chemical or physical reactions involved, the criteria for solid-state reactions, the kinetics of solid-state reactions, and the broad field of stability testing.

There is a need to develop an understanding of solid-state reactions of drugs in terms of the molecular details of the reactions. Of particular interest is the determination of the molecular parameters that can lead to retardation of the solid-state reactions of drugs and thus render drugs more stable.

It is the aim of the rest of this book to further illustrate the importance and value of molecular understanding of solid-state reactions.

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